Clinical Review Criteria
Magnetic Resonance Guided Focused Ultrasound for Treatment of Uterine Fibroids

- ExAblate 2000 Technology for Ablation of Uterine Fibroids

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Criteria
For Medicare Members

<table>
<thead>
<tr>
<th>Source</th>
<th>Policy</th>
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<tr>
<td>CMS Coverage Manuals</td>
<td>None</td>
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<tr>
<td>National Coverage Determinations (NCD)</td>
<td>Nuclear Radiology Procedure (220.8)</td>
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<td>Local Coverage Determinations (LCD)</td>
<td>Non-Covered Services (L35008)</td>
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<td>And for facility-based services billed using a UB form, see Non-Covered Services (L34886)</td>
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<td>Local Coverage Article</td>
<td>None</td>
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For Non-Medicare
There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies (and/or) provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background
Uterine fibroids (or leiomyoma) are benign tumors of the uterus with a rich blood supply that may cause excessive bleeding and pelvic pain. The prevalence of uterine fibroids is estimated to be 20-40% in women older than 35. Hysterectomy is the standard permanent treatment for women who do not have a strong desire to retain their uterus. Other treatments include watchful waiting, medical management with hormonal therapy, myomectomy (local surgical removal) and uterine artery embolization (UAE). UAE is covered for GHC members when recommended by a GHC physician.

The ExAblate 2000 system (Insightec Ltd., Israel) is a minimally invasive, uterine-sparing treatment for uterine fibroids. The system is used in conjunction with a commercially available MRI scanner, the GE Signa 1.5T MR imaging system. A special coil is required to use the GE device with the ExAblate system. The MRI is used for planning, and also for monitoring during the procedure. The treatment is also known as MR guided focused ultrasound (MRI-FUS or MRgFUS).

During the procedure, focused ultrasound waves heat the targeted fibroid tissue to approximately 65-85°C, causing cell necrosis. Over time, the necrotic tissue is absorbed by the body. The treatment can take several hours, and it requires collaboration between a gynecologist and a radiologist.

The ExAblate system was approved by the FDA in October, 2004 for ablation of uterine fibroid tissue in pre- or peri- menopausal women with symptomatic uterine fibroids who want a uterine sparing procedure. Patients must have a uterine size of <24 weeks' gestation and have completed child-bearing. Prior to commercial availability in the U.S., the ExAblate system was used in Europe (since 2002) and, to a limited extent, in Japan.
Medical Technology Assessment Committee (MTAC)

Magnetic Resonance Guided Focused Ultrasound in the Treatment of Uterine Fibroids

06/04/2008: MTAC REVIEW

Evidence Conclusion: In the FDA pivotal study in which 109 women were treated using the ExAblate 2000 technology (Stewart et al., 2006), there was a statistically significant improvement in self-reported symptoms pre- and post-treatment. The Funaki et al. (2007) case series did not report pre- and post-comparisons. 25 out of 69 women (53%) reported improving a great deal or being symptom-free 3 months after being treated. An additional 17 women (28%) said their symptoms were somewhat improved. In both studies, the main outcomes were self-report measures. A sham or comparison group is needed in this type of study to evaluate the extent to which treatment with ExAblate had a placebo effect on women’s perception of their symptoms. None of the published studies focused on objective health outcomes such as bleeding or anemia. There is insufficient evidence to draw conclusions about the safety and effectiveness of the ExAblate 2000 technology for ablation of uterine fibroids. The empirical literature consists of case series. There are no studies comparing this technology to sham treatment or other accepted treatments such as UAE and myomectomy.

Articles: The Medline search yielded 35 articles. There was also an unpublished FDA document from October 2004, entitled, “Summary of safety and effectiveness data”. The pivotal study submitted by InSightec to the FDA was a cohort study with n=109 receiving MRI-FUS with ExAblate and n=83 receiving hysterectomy. The FDA document describes pre- and post-treatment findings in each group, but does not present statistical comparisons comparing results in the two groups. Several subsequent published articles described subjective treatment effects in the 109 patients who received ExAblate in the FDA pivotal study. These include Hindley et al., 2004 (short-term outcomes) and Stewart et al., 2006 (6- and 12-month outcomes). No published articles were identified that compared the ExAblate and hysterectomy groups in the FDA pivotal study. No published randomized or non-randomized controlled studies were identified that compared ExAblate to sham or to a less invasive alternative treatment such as uterine artery embolization or myomectomy. Two studies were identified that compared different protocols of MRI-FUS. One was a small study in which one of the two groups received a GnRh agonist pre-treatment and the other evaluated compared a standard and slightly modified treatment guideline with the ExAblate system. Stewart et al. also published an article in 2007 that combined and re-evaluated data from the FDA study and other case series sponsored by Insightec. This article included selected data and post-hoc analyses which can be misleading and thus was not evaluated further. The Stewart et al., 2006 study reporting the clinical outcomes from the FDA pivotal trial was critically appraised. In addition, a case series from Japan with a reasonably large sample size was critically appraised. References are: Stewart EA et al. Clinical outcomes of focused ultrasound surgery for treatment of uterine fibroids. Fertil and Steril 2006; 85: 22-29. See Evidence Table.

The use of Magnetic resonance guided focused ultrasound in the treatment of uterine fibroids does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

Magnetic Resonance-Guided Focused Ultrasound (MRgFUS)

07/25/2016: Medical Technology Assessment Team (MTAT) Review

Evidence Conclusion: Efficacy Based on the available evidence from one RCT (Jacoby et al., 2016) and two non-randomized prospective cohort studies (Taran et al., 2009; Ikink et al., 2014), there is low quality evidence of the efficacy of MRgFUS or MR-HIFU compared to hysterectomy, myomectomy, UAE, or sham for treating uterine fibroids.

- The RCT demonstrated that MRgFUS led to fibroid volume reduction and improvements in fibroid-related symptoms and quality of life; however; these outcomes were not found to be different from the outcomes in women undergoing the sham procedure. At 24-month follow-up, 30% of patients in the MRgFUS group required re-intervention for recurrent symptoms.
- The two non-randomized cohort studies (one comparing MRgFUS to hysterectomy and one comparing MR-HIFU to UAE) found that, in general, MRgFUS/MR-HIFU led to improvements in clinical outcomes (e.g., symptom relief, quality of life). Re-intervention following MRgFUS/MR-HIFU was reported in 4% and 47% of patients in these studies, respectively.

In addition to these comparative studies, other single-arm studies evaluated the efficacy of MRgFUS for treatment of uterine fibroids:

- One technology assessment evaluating studies of MRgFUS using the ExAblate system (Hayes, Inc., 2014) determined that, overall, the quality of evidence of efficacy of MRgFUS for fibroid treatment is low. The study found generally positive clinical outcomes (e.g., reduced fibroid volume and symptoms) in studies included in the review but the need for re-intervention following MRgFUS was high, with 15% to 31% of patients requiring alternative therapy (e.g., myomectomy, hysterectomy) for persistent/recurrent symptoms. Four single-arm...
studies identified by our update search (Quinn, Vedelago, Gedroyc, & Regan, 2014; Carrasco-Choque et al., 2015; Mindjuk, Trumm, Herzog, Stahl, & Matzko, 2015; Thiburce et al., 2015) found that, in general, MRgFUS led to reduction in fibroid volume and symptom improvement. Only one study (Quinn et al., 2014) reported longer-term outcomes, with an overall re-intervention rate of 58.64% at 5 years.

**Safety/Adverse Events and Pregnancy Outcomes**

Based on the available evidence from one RCT (Jacoby et al., 2016) and two non-randomized prospective cohort studies (Taran et al., 2009; Ikink et al., 2014), there is very low quality evidence of the safety of MRgFUS or MR-HIFU compared to hysterectomy, myomectomy, UAE, or sham for treating uterine fibroids.

- The RCT published by Jacoby et al. (2016) found that women in both study groups (MRgFUS and sham) reported pain during the procedure but women treated with MRgFUS were more likely to report abdominal or pelvic pain compared to women treated with the sham procedure (83% vs. 63%, respectively). However, power to detect significant differences between groups was limited due to small sample size.
- Ikink, et al. (2014) found no serious complications or adverse events in women treated with MR-HIFU, compared with ≤10% of women treated with UAE.
- Likewise, Taran, et al. (2009) reported that, overall, women treated with MRgFUS experienced fewer clinical complications and adverse events than women who received hysterectomy.

Additional, single-arm studies have evaluated the safety of MRgFUS, as well as outcomes of unintended pregnancies following treatment with MRgFUS:

- One systematic review of studies assessing reproductive outcomes following MRgFUS (Clark, Mumford, & Segars, 2014) reported 35 published live births, with vaginal delivery occurring in 19 of 35 (53%) of post-MRGUS pregnancies; however, long-term outcomes were not assessed. The review concluded “Several case series report uncomplicated pregnancy following MRgFUS; however, results of the ongoing studies will further elucidate the utility of MRgFUS in patients planning future fertility.”
- Hayes (2014) reported that “MRgFUS with the ExAblate system appears to be relatively safe. No serious AEs were reported in the reviewed studies. Procedure-related complications include abdominal pain and discomfort, heating and burning of scarred areas of skin, skin burns, leg pain, inflammation of the fat and muscle of the abdominal wall, and bowel perforation. While MRgFUS therapy is recommended for women who have completed childbearing, the impact of this treatment on pregnancy outcomes has not been established.”
- Results from three single arm studies (Quinn et al., 2014; Mindjuk et al., 2015; Thiburce et al., 2015) indicated serious adverse events in only a few patients (<6.5% across studies). In terms of pregnancy complications, spontaneous abortion occurred in 1 out of 15 patients who had an unintended pregnancy during the study period.

**Overall Conclusion:** The studies identified in this assessment have limitations that make it difficult to have confidence in the estimates regarding efficacy and safety of MRgFUS or MR-HIFU for treatment of uterine fibroids. Given the small sample sizes of most of the studies, the lack of evidence on long-term health and pregnancy outcomes, and a substantial concern about the existence of confounding in study design:

1. There is low quality evidence that MRgFUS or MR-HIFU is as efficacious as hysterectomy and UAE for treating symptomatic uterine fibroids. The available evidence suggests MRgFUS or MR-HIFU is less efficacious than hysterectomy and UAE for treating symptomatic uterine fibroids.
2. There is very low quality evidence that MRgFUS or MR-HIFU is as safe as hysterectomy and UAE for treating symptomatic uterine fibroids.

The potential benefits of MRgFUS or MR-HIFU for treating uterine fibroids should be weighed against the potential harms (e.g., need for re-intervention following treatment). Additional large, high quality longitudinal studies are needed to assess the long-term efficacy and safety of MRgFUS or MR-HIFU for treating uterine fibroids.

**Articles:** Two systematic reviews (Clark, 2014; Canadian Agency for Drugs and Technologies in Health (CADTH), 2016 (Chen, Pitre, Kaunelis, & Singh, 2016)) and one technology assessment (Hayes, Inc., 2014) addressing efficacy and/or safety of MRgFUS or MR-HIFU were identified. The most comprehensive systematic review of comparative studies involving any type of MRgFUS versus hysterectomy, myomectomy, or UAE is from CADTH. We therefore used the CADTH report as our primary evidence source. Our update search identified one pilot randomized controlled trial (PROMiSe Trial; Jacoby, et al., 2016) that assessed the efficacy and safety of MRgFUS compared to a sham procedure. Therefore, a total of three comparative studies (two from the CADTH report and one from our update search) were selected for inclusion in the SCPMG EBM assessment. CADTH (2016) found that MRgFUS (or MR-HIFU) was associated with more re-interventions but also fewer complications compared with hysterectomy and UAE. The review included RCTs, non-randomized studies, and economic evaluations assessing the clinical effectiveness and safety of uterine-preserving interventions in women with symptomatic uterine fibroids. Interventions of interest included myomectomy, myolysis, UAE, uterine artery occlusion (UAO), or endometrial ablation. They were compared with each other or with hysterectomy. The search
for health technology assessments, systematic reviews, meta-analyses, and guidelines was limited to documents published since January 1, 2005, while the search for randomized controlled trials (RCTs), controlled clinical trials, cohort studies, and economic studies was not limited by publication year. A total of two non-randomized observational studies comparing MRgFUS versus hysterectomy and UAE (Taran et al., 2009 and Ikink et al., 2014, respectively) were reviewed and appraised (last CADTH search date: November 24, 2015).

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<tr>
<th>Date Created</th>
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<th>Date Last Revised</th>
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<tr>
<td>07/17/2008</td>
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MPC Medical Policy Committee

<table>
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<tr>
<th>Revision History</th>
<th>Description</th>
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<tr>
<td>09/08/2015</td>
<td>Revised LCD L34886 and L35008 Non-Covered Services.</td>
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<tr>
<td>02/13/2017</td>
<td>Added KP MTAT Review</td>
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**Codes**

0071T, 0072T